

What is claimed is:

Sub  
A1  
1. A method for the treatment of a tumor in a mammal, wherein the tumor is characterized by the overexpression of an ErbB receptor and does not respond, or responds poorly, to treatment with an anti-ErbB antibody, comprising administering to  
5 the mammal a therapeutically effective amount of a conjugate of the anti-ErbB antibody with a maytansinoid.

2. The method of claim 1 wherein the mammal is human.

10 3. The method of claim 2 wherein the ErbB receptor is selected from the group consisting of ErbB1 (EGFR), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4).

4. The method of claim 3 wherein the anti-ErbB antibody is a growth inhibitory antibody.

Sub  
A2  
15 5. The method of claim 3 wherein the anti-ErbB antibody induces cell death.

6. The method of claim 3 wherein the anti-ErbB antibody induces apoptosis.

20 7. The method of claim 3 wherein the antibody is an anti-ErbB2 antibody.

Sub  
A3  
8. The method of claim 7 wherein the tumor is cancer.

25 9. The method of claim 8 wherein the cancer is selected from the group consisting of breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer.

10. The method of claim 9 wherein the cancer is breast cancer.

30 11. The method of claim 10 wherein the breast cancer overexpresses ErbB2 at a 2+ level or more.

12. The method of claim 11 wherein the breast cancer overexpresses ErbB2 at a 3+ level.

5 13. The method of claim 12 wherein the breast cancer is a metastatic breast cancer.

14. The method of claim 12 wherein the antibody has a biological characteristic of a 4D5 monoclonal antibody.

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15. The method of claim 14 wherein the antibody binds essentially the same epitope as a 4D5 monoclonal antibody.

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16. The method of claim 14 wherein the antibody is the monoclonal antibody 4D5 (ATCC CRL 10463).

17. The method of claim 14 wherein the antibody is humanized.

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18. The method of claim 17 wherein the antibody is selected from the group consisting of humanized antibodies huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8 (HERCEPTIN®).

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19. The method of claim 18 wherein the antibody is humanized antibody huMAb4D5-8 (HERCEPTIN®).

20. The method of claim 3 wherein the antibody is an antibody fragment.

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21. The method of claim 20 wherein the antibody fragment is selected from the group consisting of a Fab, Fab', F(ab')<sub>2</sub>, F<sub>v</sub> fragment, diabody, linear antibody, and single-chain antibody molecule.

Sub A5  
5 22. The method of claim 3 wherein the maytansinoid is maytansine.

23. The method of claim 3 wherein the maytansinoid is maytansinol.

24. The method of claim 3 wherein the maytansinoid is a maytansinol ester.

25. The method of claim 24 wherein the maytansinoid is a C-3 ester of maytansinol.

Sub B2  
10 26. The method of claim 25 wherein the maytansinoid is DM1 shown in Figure 1.

Sub A6  
15 27. The method of claim 3 wherein the antibody and maytansinoid are conjugated by a bispecific chemical linker.

28. The method of claim 27 wherein said chemical linker is N-succinimidyl-4-(2-pyridylthio)propanoate (SPDP) or N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

Sub A7  
20 29. The method of claim 3 wherein the antibody and maytansinoid are conjugated by a linking group selected from the group consisting of a disulfide, thioether, acid labile, photolabile, peptidase labile, and esterase labile group.

25 30. The method of claim 29 wherein the linking group is a disulfide or a thioether group.

31. The method of claim 30 wherein the linking group is a disulfide group.

30 32. The method of claim 1 wherein the conjugate comprises 1 to about 10 maytansinoid molecules per antibody molecule.

33. The method of claim 32 wherein the conjugate comprises from about 3 to about 5 maytansinoid molecules per antibody molecule.

Sub A8  
5 34. The method of claim 7 further comprising the administration of a second antibody which binds ErbB2.

35. The method of claim 34 wherein the second antibody comprises monoclonal antibody 2C4 or humanized 2C4.

Sub B3  
10 36. The method of claim 34 wherein the second antibody is humanized antibody, huMAb4D5-8 (HERCEPTIN<sup>®</sup>).

15 37. The method of claim 1 wherein treatment with the conjugate is followed by treatment with an unconjugated anti-ErbB antibody.

38. The method of claim 32 wherein the conjugate is administered weekly at a dose of 0.1 to 10 mg/kg body weight.

20 39. The method of claim 38 wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

40. The method of claim 33 wherein the conjugate is administered weekly at a dose of 1 to 3 mg/kg body weight.

25 41. The method of claim 40 wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

Sub A9  
30 42. The method of claim 7 wherein the conjugate is administered weekly at a dose of 0.1 to 5 mg/kg body weight for 4 to 6 weeks, followed by maintenance treatment with unconjugated anti-ErbB2 antibody.

Sub B4  
43. The method of claim 42 wherein the unconjugated antibody is humanized antibody huMAb4D5-8 (HERCEPTIN®) or humanized 2C4.

44. The method of claim 34 wherein said second antibody is conjugated with a  
5 cytotoxic agent.

45. The method of claim 44 wherein the cytotoxic agent is a maytansinoid.

Sub A10  
46. The method of claim 7 wherein said treatment has an improved objective  
10 response rate compared to treatment with huMAb4D5-8 (HERCEPTIN®) alone.

47. The method of claim 7 wherein said treatment has a longer duration of response than treatment with huMAb4D5-8 (HERCEPTIN®) alone.

48. The method of claim 7 wherein said treatment results in increased survival  
15 of the mammal treated compared with treatment with huMAb4D5-8 (HERCEPTIN®) alone.

49. An article of manufacture comprising a container and a composition  
20 contained therein, wherein the composition comprises an anti-ErbB antibody-maytansinoid conjugate, and further comprising a package insert or label indicating that the composition can be used to treat cancer characterized by the overexpression of an ErbB receptor.

50. The article of manufacture of claim 49 wherein said package insert or  
25 label indicates that the composition can be used to treat cancer characterized by the overexpression of an ErbB2 receptor.

51. The article of manufacture of claim 50 wherein the cancer is breast cancer.

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52. The article of manufacture of claim 50 wherein the cancer is characterized by the overexpression of an ErbB2 receptor at a 2+ level or above.

53. The article of manufacture of claim 52 wherein the cancer is characterized  
5 by the overexpression of an ErbB2 receptor at a 3+ level.

54. The article of manufacture of claim 52 wherein said cancer is an aggressive form of metastatic breast cancer.

52. The article of manufacture of claim 50 wherein the cancer is characterized by the overexpression of an ErbB2 receptor at a 2+ level or above.